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## lntroduction

Outsourcing of clinical research projects is not something new, having been employed by pharmaceutical companies throughout the 1970s and 1980s, but the use of outsourcing has seen a steep increase since the 1990s. Contract research surveys estimate that the number of clinical and preclinical Clinical Research Organizations (CROs) have risen from about 100 in the US and 100 in Europe in 1981 to approximately 380 and 650 in the US and Europe, respectively, by 2003 (Hughes, 2004). Furthermore, the global value of the CRO market increased from about $1.2b in 1987 to $3b in 1993 (Hughes, 2004). In terms of the level of outsourcing, Hughes estimated that by 1993 over 90<\'o of companies engaged in some form of outsourcing. Activities range from limited outsourcing of clinical trials to extensive outsourcing of preclinical evaluations, study design, clinical trial management, data collection, biostatistical analysis and completing product regulatory requirements (LeadDiscovery, 2006).

Given the widespread use of outsourcing, it is a topic that most people involved in clinical research projects need to have some knowledge and awareness of.

There are two broad types of outsourcing: strategic and tactical. Tactical outsourcing is opportunistic and used as a short-term fix. Strategic outsourcing occurs in long-term arrangements that are typical of partnerships. Contracts are standardized, working practices are agreed and fully understood and planning isa shared activity between the parties. Pharmaceutical companies will discuss their pipeline of studies and CROs will be equally open about their resource requirements. Both parties of the outsourcing decision,
e.g. the pharmaceutical company who is the client and the CRO who is the contractor, share complementary goals. High-level strategic outsourcing involves forming long-term partnerships with single CROs. Such outsourcing aims to develop relationships based on trust and long-term business stability for both client and CRO (Hughes, 2004). By developing such a relationship, the pharmaceutical company and the CRO can overcome the problems associated with the principal/agent arrangement, such as the principal thinking the agent is trying to maximize their short-term profits through the addition of unnecessary work, or the agent thinking the principal is trying to take short- term advantage through the addition of work not in the original specification.

Whilst strategic outsourcing might have theoretical and practical benefits to companies, it's not commonly used in our industry. For many organizations, such as small biotech’s, there is simply not enough future work or enough money to invest in these types of relationships. Therefore, whilst noting the existence of strategic outsourcing, the remainder of this guide wilI focus on tactical outsourcing. (Though it is hoped those with strategic partnerships in place will find the material in this booklet useful, in dealing with the more tactical end of the outsourcing spectrum.)

## Chapter I - The Outsourc in Decision

Before making a decision to outsource a clinical trial it is worth bearing in mind the character

of tactical outsourcing, as there isa potential for problems to arise due to the very nature of the outsourcing relationship.
Tactical outsourcing is more opportunistic than strategic outsourcing and is often used as a short-term fix for problems such as a lack of internal resource within a pharmaceutical company to manage a specific clinical
trial. Tactical outsourcing implies transactional relationships, with the nature of the transaction being formed by the specific contract set up for each project. As such, it involves a classic 'Principal/Agent' relationship, with the pharmaceutical company being the principal who sponsors the agent, the CRO, to undertake work on their behalf. The contracts associated with tactical outsourcing are variations on fixed price and variable [fee-for-service), with the most common form of contract being fixed. Regardless of contract
type, there is also an inherent limitation associated with all principal/agent relationships. Namely, that the relationship is vulnerable to the 'principal/agent problem', where the interests of the principal [in this case the pharmaceutical company/sponsor) and agent (CRO) may be misaligned and they will each then act in their own best interest [Lovallo and Sibomy, 2006). A climate of mistrust can quickly develop as the pharmaceutical company, who is not communicated to about the day-to-day decisions made during the clinical trial, starts to question the motives of the CRO. Therefore you will need to be aware that
if these relationships are not properly set up and managed, they have a
propensity to go wrong
Before making a decision to outsource, it is also worth thinking about the long term. Strategic and tactical outsourcing is linked with the type of relationships that you have between the client and the sub-contractor. Over time this relationship can develop from supplier, to preferred supplier and finally to partner. In a similar fashion, so the outsourcing arrangements can change from tactical to strategic, as shown in Figure 1.1.
Figure 1.1 : The Spectrum of Relationships
Developing relationship

Supplier
Tactical

Prefered Supplier

Strategic

The decision has been made to outsource a specific trial. The next step after decision-making is to consider a number of key questions that need answering before a specific CRO is selected to run the trial.

Before CRO Selection - Key Questions
In order to minimize the likelihood of problems occurring after a clinical trial has been outsourced to a CRO, it is vital that attention is paid to answering some key questions. Planning can never start too early and before CRO selection it is important that the project is clearly defined. The pharmaceutical company needs to have a clear idea of what it's trying to achieve. Clarity can be achieved by answering the following questions:
- What are the Key Performance Indicators (KPls)?
- What are the deliverables?
- What are the expectations of the various stakeholders?
- What are the risks and how can they be managed7 We will now consider each of these questions in turn.

What are the Key Performance Indicators?
Key Performance Indicators (KPls) are 'measurable indicators that will be used to report progress that is chosen to reflect the critical success factors of the project' (APM, 2000)
In clinical research projects, the KPls are usually associated with achieving time, quality and cost objectives; the 'Iron Triangle' or 'triple Constraint' that applies to all projects. Measures will include: adherence to budgets, delivery of contracted items and adherence to schedule.
The KPls need to be defined at the early project planning stage, before the decision to outsource to a particular CRO has been made.
At first sight you may see the KPls as all equally important, but their importance will vary depending on the type of clinical trial. A pivotal phase Ill study would certainly need to emphasis KPls related to quality and time, but is it appropriate to give cost-related KPls equal

importance? At this stage of product development the most expensive risks are related to poor quality and project delays or overruns. If the net present value (NPV) of the project is calculated, then the cost of running the project pales into insignificance compared to losses incurred as a result of late entry into the market. This suggests that the time and quality-related KPIs need prominence over cost- related ones. Conversely, if the project is a phase IV marketing exercise, then
cost may be much more important than time and quality; as it may not require 100% source document verification (SDV).
The key fact is that the sponsor needs to understand which KPIs are important and, when selecting a CRO, communicate that information so that the CRO understands what is important and can ensure they deliver against them.

What are the Key Deliverables?
Each study also has a set of key deliverables which also need to be defined at an early stage. Deliverables are the 'end products' of a project or 'the measurable results of intermediate activities within the project organization' [APM, 2000).
Care needs taking in defining deliverables. Although the term deliverable is often used in clinical trial environments in reality there is often a lack of clarity in terms of what is meant by a deliverable. For example, the number of patients recruited is often given as an example of a deliverable, yet this is really a milestone that, in some cases, can give a misleading impression
of project progress. Although the number of patients recruited is of interest, in itself it does not always mean that the project is on track. Even if patient recruitment is on or ahead of schedule, it does not guarantee that the case report forms [CRFs) associated with each patient recruited are of a sufficient quality or that the forms have been collected from the investigational site and entered onto the central database in a timely fashion.
The key is to establish the true deliverable, in the sense that it provides unambiguous evidence of progress. Therefore, 'final protocol approved in writing' isa deliverable, as the approval can be verified by the signatures of the relevant parties. Likewise an activity such as 'investigator meeting' is mapped to a deliverable 'number of investigator meetings documented' that can be verified through the number of meetings that have the accompanying formal documentation adequately completed. Deliverables
need to be distinguished from activities. The design of the protocol, protocol familiarization and the review of protocol translations are examples of activities. All these activities lead to the deliverable 'final protocol approved in writing'. During the definition of a deliverable, consider the quality. For example, a deliverable like 'final protocol approved in writing' will probably go through various stages like draft 1, draft 2, and final draft, before the approval of the final protocol. At all or any of these stages quality parameters can be applied. For example, the protocol cannot be signed off until it has been approved by a panel of experts, etc.
Examples of deliverables are shown in Table 1.1. Most of the deliverables shown are related to activities specifically linked to undertaking the clinical trial, such as final protocol approved in writing· and "number of investigator meetings documented''. In addition to these project-related deliverables, project management related deliverables may also be established. "Initial project
plan signed off, "project risk management plan formally approved" and "Lessons learnt report formally accepted" are examples of project management deliverables.

Table 1.1: Example list of Deliverables

| Deliverable |
| --- |
| Final Protocol approved in writing |
| Final CRF approved in writing |
| Initial Project Plan signed off |
| Final Analysis Plan signed off |
| Project Risk Management Plan formally approved |
| Number of minutes of project review meetings approved |
| Final list of investors Provided |
| Number of investigator Meetings documented |
| Number of Sites Evaluated formally |
| Number of formal Site Set-ups completed |
| Number of CRF pages monitored and in-house |
| Number of Sites formally Closed |
| Lessons Learnt Report formally accepted |

Deliverables have many uses. In particular they are instrumental in the measurement of project progress and can also be used as an alternative to milestones in payment schedules. At this pre-selection of CRO stage, as was the case with the KPIs, it is important for the sponsor to

agree what deliverables will be expected to be provided as part of the contract.

Who are the Key Stakeholders and what is their Power/Interest?

Stakeholders are people that are involved or interested in your clinical trial. They are normally classified by their power and their interest. The most important stakeholders are those with high salience, e.g. they have power to influence the outcome and they have a high degree of interest in the trial. These stakeholders are key players. At the other end of the salience scale are those with little power and little interest. Different tactics will be needed depending upon the level of salience that characterizes a specific stakeholder.

Figure 1.2 represents a stakeholder analysis of a typical phase Ill study, using a mind mapping technique. We have included some of the key interactions, but by no means all. The site investigator is obviously a key player. They have both a high level of interest (a major reason for them being involved) and, of course, high power, since they will be ultimately responsible for recruiting the subjects. They have power in another sense as well, since they are potential customers. At this stage you may wish to ask the question: "Who should be responsible for ensuring that investigator needs are met?" It may be that this area is one that you do not wish to transfer to a third party.

What does the Risk Analysis tell us?

There are many excellent publications on Project Risk Analysis and Management [PRAM), as well as PRAM guides published by the US-based Project Management Institute(PMI) and the UK-based Association for Project Management [APM); [see the bibliography) so we will not spend time in describing the PRAM process in detail. We will instead highlight the need to consider both risks and opportunities when deciding to which CRO we will outsource the trial.

Project risk is the 'combination of the probability, or frequency of occurrence, of a defined threat or opportunity and the magnitude of the consequences of the occurrence' (APM, 2000). This definition recognizes that uncertain events are not always threats, they can also be opportunities, e.g. the threat of not recruiting enough patients within the agreed timeline may result in the initiating of extra sites. This in turn may present you with an opportunity to recruit those patients more quickly than planned. Whether it is a threat or an opportunity, planning is required to reduce the threat or exploit the opportunity. In general this is not an activity that you should pass on to your CRO. Risk plans often require extra resource in terms of people and money. The example above of increasing the number of investigational sites, to ensure that the patient recruitment target is met, will require extra resource. It may not be in the best interests of a CRO involved in a competitive bid to highlight this extra cost. Risk analysis should be an ongoing process; however, it should start with the sponsor at the pre-CRO selection stage and include all the risks and opportunities of working with their suppliers.

## Chapter 2 - Finding a CRO

Having considered issues associated with KPls, deliverables, stakeholders and risk, the next step is to find a CRO that best fits your requirements. Figure 2.1 shows the outline process for the selection of a CRO. (The authors are grateful to the Pharmaceutical Contract Management Group (PCMG) Working Party for making this diagram available.) The PCMG Working Party is drawn from both the pharmaceutical and CRO industry and represents their current thinking.

As stressed in the previous chapter, before the selection process starts the pharmaceutical company will have a clear idea of what it is looking for in the trial and, hence, what it wants from its CRO. At the planning stage, first box at top left of Figure 2.1, it is essential to establish the added values you wish obtain from your sub-contractor. For example, if sites in Scandinavia are important, then the CRO's ability to operate effectively in northern Europe needs to be assessed. If therapeutic experience is important, the knowledge and backgrounds of the CRO team members will need to be assessed. There are various methods of generating the areas where you require added value, including the following:

- Interviews
- Brainstorming
- Mind Mapping
- Check & Prompt lists
- Delphi Technique.

Once you have generated the list, it is useful to attach a level of importance to each item. One method for displaying the information about CRO requirements. based on the analysis, is a radar plot. In the example below (Figure 2.2) each item is scored on a radar plot using a scale from 1 to 10 (where 1 = least important and 10 = most important). In this example there are nine areas where value-added is required; the most important being the quality of project planning (score 10) and the least important being the price (score 3).

Some ti me and effort also needs to be spent on how these added values are to be measured. Some, such as geographic coverage may be relatively easy to measure. For example, if the CRO can monitor 90% of your site with locally based Clinical Research Associates (CRAs) then they would

score 9 on the above scale. With therapeutic experience some assessment of the actual team members' experience would be required. A team member with no therapeutic experience would score O; those with current experience would score 10; those with experience within the last year would score 9,etc. The average of all of thekey staffs individual scores would be the overall score.